META-ANALYSIS

Peripheral vasoconstriction induced by β-adrenoceptor blockers: a systematic review and a network meta-analysis

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AIM

Peripheral vasoconstriction has long been described as a vascular adverse effect of β-adrenoceptor blockers. Whether β-adrenoceptor blockers should be avoided in patients with peripheral vascular disease depends on pharmacological properties (e.g. preferential binding to $β_1$-adrenoreceptors or intrinsic sympathomimetic activity). However, this has not been confirmed in experimental studies. We performed a network meta-analysis in order to assess the comparative risk of peripheral vasoconstriction of different β-adrenoceptor blockers.

METHOD

We searched for randomized controlled trials (RCTs) including β-adrenoceptor blockers that were published in core clinical journals in the Pubmed database. All RCTs reporting peripheral vasoconstriction as an adverse effect of β-adrenoceptor blockers and controls were included. Sensitivity analyses were conducted including possibly confounding covariates (latitude, properties of the β-adrenoceptor blockers, e.g. intrinsic sympathomimetic activity, vasodilation, drug indication, drug doses). The protocol and the detailed search strategy are available online (PROSPERO registry CRD42014014374).

RESULTS

Among 2238 records screened, 38 studies including 57 026 patients were selected. Overall, peripheral vasoconstriction was reported in 7% of patients with β-adrenoceptor blockers and 4.6% in the control groups ($P < 0.001$), with heterogeneity among drugs. Atenolol and propranolol had a significantly higher risk than placebo, whereas pindolol, acebutolol and oxprenolol had not.

CONCLUSION

Our results suggest that β-adrenoceptor blockers have variable propensity to enhance peripheral vasoconstriction and that it is not related to preferential binding to $β_1$-adrenoceptors. These findings challenge FDA and European recommendations regarding precautions and contra-indications of use of β-adrenoceptor blockers and suggest that β-adrenoceptor blockers with intrinsic sympathomimetic activity could be safely used in patients with peripheral vascular disease.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
- β-adrenoceptor blockers are known to induce peripheral vasoconstriction, probably according to their pharmacological properties (e.g. preferential binding to β1-adrenoreceptors, intrinsic sympathomimetic activity or vasodilator effect). However, this has never been confirmed in experimental studies.

WHAT THIS STUDY ADDS
- Our results suggest that β-adrenoceptor blockers have variable propensity to enhance peripheral vasoconstriction. Moreover, ancillary properties of β-adrenoceptor blockers widely influence this peripheral vasoconstriction: ISA and vasodilator effect are protective, whereas preferential binding to β1-adrenoreceptors does not protect from peripheral vasoconstriction.
- These findings challenge FDA and French recommendations regarding precautions and contra-indications of use of β-adrenoceptor blockers, and suggest that β-adrenoceptor blockers with intrinsic sympathomimetic activity could be safely used in patients with Raynaud's phenomenon.

Introduction

β-adrenoceptor blockers have long been known to cause drug-induced peripheral vasoconstriction, especially Raynaud's phenomenon (RP), which was described as an adverse effect of β-adrenoceptor blockers 40 years ago [1]. Among the aetiologies of the syndrome, β-adrenoceptor blockers have usually appeared as the primary cause of drug-induced RP in recent state-of-the-art reviews and textbooks [2–6]. However, little is known about the exact prevalence of β-adrenoceptor blocker induced peripheral vasoconstriction. Analysis of the Framingham heart study identified β-adrenoceptor blocker use as the most common cause of secondary RP (34.2% of secondary RPs) [7]. More recently, a meta-analysis including 13 studies found a prevalence of RP of 14.7% in patients receiving β-adrenoceptor blockers [8]. However, the number of included studies was low and this simple meta-analysis did not permit to hierarchizing the vasoconstrictor effect of the different β-adrenoceptor blockers. The exact mechanism leading to peripheral vasoconstriction induced by β-adrenoceptor blockers remains incompletely understood. Antagonism of β_2-adrenoceptors, which are responsible for peripheral arteriolar vasodilatation, has long been thought to be the main mechanism. This led to the contra-indication of non-selective β-adrenoceptor blockers in patients with RP. However, this hypothesis is challenged by clinical observations of RP occurring in patients taking β-adrenoceptor blockers with higher affinity for β_1-adrenoceptors [1, 9]. In addition, in patients with primary RP, no differences in skin or muscular blood flow could be detected between propranolol, a non-selective β_2-adrenoceptor blocker and metoprolol, a β_1-adrenoceptor blocker [10]. Moreover, the involvement of β_2-adrenoceptors in the pathogenesis of RP is not currently upheld [11].

Another hypothesis to explain peripheral vasoconstriction due to β-adrenoceptor blockers would involve the vasoconstrictor sympathetic reflex mediated by baroreceptors in response to the decrease in cardiac output following β-adrenoceptor blocker intake [12]. In accordance with this hypothesis, β-adrenoceptor blockers with intrinsic sympathomimetic activity (ISA) have a less pronounced effect on cardiac output, and may even decrease peripheral resistance during chronic treatment, therefore inducing less peripheral vasoconstriction [12]. However, limited evidence supports this hypothesis in patients with Raynaud's phenomenon, and available data are conflicting [13–15].

The paradox is that a considerable number of large, randomized, controlled trials have been conducted in the past decades that should provide sufficient evidence to clarify the implication of β-adrenoceptor blockers in induced peripheral vasoconstriction, such as RP. In the past few years, the development of sophisticated methods such as the combination of direct and indirect comparisons in network meta-analyses has been successfully applied to identify class adverse drug events [16].

Our objective in the present work was therefore to perform a systematic review and a network meta-analysis of randomized clinical trials to assess the effect of β-adrenoceptor blockers on peripheral vascular disease. We aimed at comparing the risk of peripheral vasoconstriction induced by the different β-adrenoceptor blockers according to their pharmacological properties (ISA, β_1-selectivity, vasodilators and non-selective).

Methods

This systematic review complies with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement guideline [17]. The protocol and systematic search strategy of the review has been documented online before starting the study (PROSPERO registry, CRD42014014374).

Objectives and outcomes

The primary objective of our study was to assess and compare the effect of β-adrenoceptor blockers on peripheral vascular disease.

Secondary objectives were to compare the risk of peripheral vasoconstriction induced by the different β-adrenoceptor blockers according to their pharmacological properties (ISA, β_1-selectivity, vasodilators and non-selective), assess the influence of the year of study publication, the latitude, the way of reporting RP, the dosage and indication for β-adrenoceptor blockers on the risk of peripheral vasoconstriction.

Study identification, selection and data extraction

We searched for randomized controlled trials (RCTs) including β-adrenoceptor blockers that were published in core clinical journals in the Pubmed database. The following terms were sought: acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, celiprolol, labetalol, metoprolol, nadolol, nebivolol, oxprenolol, pindolol, propranolol, sotalol and β-adrenoceptor blockers.

Applied filters were (Comparative Study [ptyp] OR Clinical Trial[ptyp]) AND jsubsetaim[text]. We also searched Google Scholar, the reference lists of relevant Cochrane reviews [18–20] and the reference list of the Trial Result-centre (http://www.trialresultscenter.org). There was no restriction on language or publication date. One reviewer (CK) screened titles and abstracts for inclusion. Then two authors (MR and CK) independently reviewed the full text of potentially relevant articles to check inclusion criteria using a standardized form. Eligibility criteria included parallel or crossover RCTs comparing the previously listed β-adrenoceptor blockers to control groups (placebo or any active comparator), for at least 4 weeks and reporting RP or any relevant symptom related to peripheral vasoconstriction. Despite the high prevalence of RP, standardized diagnostic criteria have not been used in these trials. Therefore, we used the term 'peripheral vasoconstriction' rather than 'Raynaud's phenomenon'.

Independent assessment of risk of bias was made by the same reviewers according to the Cochrane Handbook for Systemic Reviews of Interventions [21]. The risk of bias was rated as low, unclear or high for the following items: randomization, blinding, incomplete outcome data, selective reporting. The overall risk of bias for each trial was defined as high risk if more than three high risk criteria were met, moderate risk if two to three high risk criteria were met and low risk if one or less high risk criterion was met.

Then, the same two reviewers independently extracted data and appraised the quality and content of included studies using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) recommendations for network meta-analysis [22]. These recommendations permit to appraise the quality of each direct and indirect pairwise comparisons of the network meta-analysis considering the average risk of bias [23], inconsistency [24], indirectness [25], imprecision [26] and publication bias [27]. Finally we rated their quality as very low, low, moderate or high. Special attention was paid to the way used to record the side effects (spontaneous reporting, medical visit or questionnaire).

The following data were extracted: year, country(ies) and latitude where the study was conducted, sample size, methodology, Raynaud' phenomenon as a non-inclusion criteria in the trial, indication of the β-adrenoceptor blocker, follow-up period, β-adrenoceptor blocker dosage and treatment duration, nature of the peripheral vascular effect reported and frequency of outcomes (prevalence and/or withdrawals).

Statistical analysis

The primary objective was to compare the number of events in the different treatment arms with a frequentist approach. We used an arcsine transformation as it enables one to include empty cells in the analysis (i.e. taking into account study arms without any event), without continuity corrections [28]. We also provided odds ratios (OR) for easier interpretation, with a + 1 continuity correction for empty cells. Meta-regressions were performed to take into account covariates of interest, i.e. the year of study publication, the latitude, the way of reporting RP, as well as the dosage and indication for β-adrenoceptor blockers. A Bayesian approach was used to compute the rankograms as well as indirect effects (using the node-splitting algorithm). The rankograms

represent the probability of each β-adrenoceptor blocker to be the greatest inducer of peripheral vasoconstriction.

Statistical analysis was performed with R statistical software (version 3.2.0). The metafor package (v1.9–4, www.metafor-project.org) was used for frequentist analyses and the gemtc package (with the rjags Gibbs sampler) [29] for the Bayesian approach. We used a Mantel–Haenszel method with a random effect model to provide pooled OR of the risk of peripheral vasoconstriction according to the pharmacological properties of β-adrenoceptor blockers *vs.* placebo, using RevMan (Version 5.1, The Cochrane Collaboration, 2011). Confidence or credibility intervals are given for all measures and represented in forest plots. We used *t*-test to compare frequencies between groups when necessary. All tests and confidence or credibility intervals were two-sided. *P* values <0.05 were considered as significant.

Results

Characteristics of studies and patients

The literature search yielded a total of 2238 references. The main reasons for excluding records were that studies were *in vitro* studies, or were not randomized clinical trials, or were RCTs that did not report the incidence of peripheral vasoconstriction. Thirty-eight studies finally fulfilled the eligibility criteria [30–67]. (Figure 1).

All studies were RCTs with study duration ranging from 4 to 468 weeks and included a total of 57 026 patients. Most of the trials were multicentre and parallel, conducted in Europe or North America, examined a β-adrenoceptor blocker as an antihypertensive treatment and included an active comparator (27/38). For more than half of them, the presence of RP was a non-inclusion criterion (20/38). The characteristics of included studies are presented in Table 1.

The risk of bias is reported in supplementary on-line Figure S1. Eight studies were considered as having a high risk of bias.

Overall prevalence of peripheral vasoconstriction

The prevalence of peripheral vasoconstriction was highly dependent on the way in which adverse events were reported: 13.47% with a questionnaire (systematic approach) and 6.02% for spontaneous reports. In the placebo group, the prevalence was 8.1% with a questionnaire and 4.84% with spontaneous reporting.

Network and methodological quality of available comparisons

Thirty-four direct comparisons between β-adrenoceptor blockers and controls were available. Controls mostly included placebo, angiotensin-converting enzyme blockers/angiotensin receptor blocker, α-adrenoceptor blockers and thiazide diuretics. The network of available comparisons is represented in Figure 2.

The quality of evidence according to GRADE recommendations are presented in Supplementary Table S1. Discrepancies between the mean qualities of evidence for each β-adrenoceptor blocker were obvious and are presented in Table 2. When combining β-adrenoceptor blockers
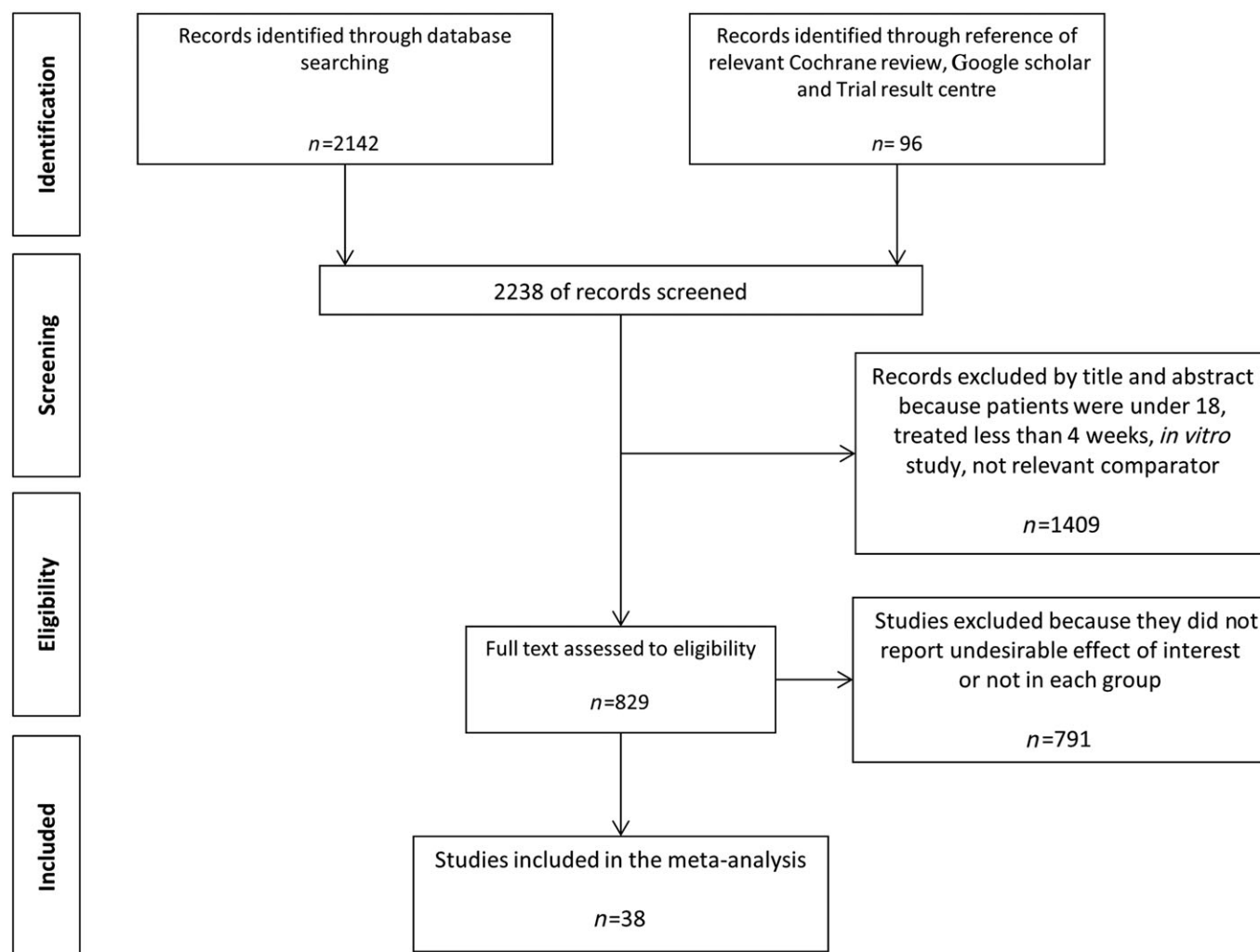
Figure 1

PRISMA flow diagram

depending of their pharmacologic properties overall mean qualities of each group were moderate for β-adrenoceptor blockers owning ISA and β_1-selectivity, just below the moderate threshold for non-selective β-adrenoceptor blockers and low for vasodilator β-adrenoceptor blockers. Moreover, the percentages of high qualities studies included in each group were comparable, except for the vasodilator group (Table S3).

Peripheral vasoconstriction induced by β-adrenoceptor blockers

The prevalence of peripheral vasoconstriction among patients treated with β-adrenoceptor blockers was 7% (1966/28 072), whereas 4.6% (555/12 060) and 1.7% (305/17 492) of patients treated with placebo or active control experienced peripheral vasoconstriction, respectively ($P < 0.001$).

The network meta-analysis of direct and indirect comparisons between the different β-adrenoceptor blockers revealed differences between drugs (Figure 3, supplementary Figure S2). Propranolol (moderate quality evidence) and atenolol (moderate quality evidence) significantly increased the risk of peripheral vasoconstriction. Continuity correction

for empty cells allowed calculating ORs of 3.0 (1.4–6.6) and 2.0 (0.9–4.7) for propranolol and atenolol, respectively.

Influence of pharmacologic properties of β-adrenoceptor blockers on peripheral vasoconstriction

We categorized β-adrenoceptor blockers into four non-exclusive groups (non-selective, β_1-selective, ISA and vasodilators), depending on their secondary properties (presented in Table 2). The OR of peripheral vasoconstriction in each group was 2.53 (1.39–4.61), 1.67 (1.29–2.17), 1.24 (0.7–2.19), respectively. Only β_1-selective and non-selective β-adrenoceptor blockers were associated with an increased risk of peripheral vasoconstriction when compared with placebo (Figure 4).

Sensitivity analyses

Univariate meta-regressions did not show any significant effect of study latitude (P = 0.18), drug indication [hypertension (P = 0.24), ischaemia (P = 0.27), other (P = 0.71)], drug doses [low (P = 0.67), normal (P = 0.86), high (P = 0.82)],

Table 1

Study characteristics

Study	Country	Indication	Treatment	n	Methodology	Exclude RP	Exposure (weeks)	Double-blind	Peripheral vasoconstriction symptom
DiBianco et al. [30]	USA	Angina	Acebutolol, propranolol, placebo	46	Crossover	No	9	Yes	Cold extremities
Dahlöf et al. [31]	UK–Scandinavian	HT	Atenolol, CCB	19 257	Parallel	Yes	287	No	Peripheral coldness
Dahlöf et al. [32]	USA-UK-Scandinavian	HT	Atenolol, ACE/ARB	9193	Parallel	Yes	209	Yes	Cold extremities
Talseth et al. [33]	Norway	HT	Atenolol, α-adrenoceptor blocker	164	Parallel	No	157	Yes	Peripheral ischaemia
NASR Committee [34]	UK	HT	Atenolol, CCB	410	Parallel	Yes	12	Yes	Peripheral ischaemia or pain
Ott et al. [35]	Denmark	HT	Atenolol, α-adrenoceptor blocker	126	Parallel	No	20	Yes	Cold extremities
Fairhurst [36]	International	HT	Atenolol, bevantolol, placebo	229	Parallel	No	12	Yes	Peripheral vascular side effect
Helgeland et al. [37]	Norway	HT	Atenolol, ACE/ARB, thiazide	400	Parallel	Yes	14	Yes	Cold extremities
Rubin et al. [38]	UK	HT	Atenolol, placebo	85	Parallel	Yes	36	Yes	Raynaud's phenomenon
Julian et al. [39]	UK	MI	Sotalol, placebo	1456	Parallel	No	26	Yes	Cold extremities
Hansteen et al. [40]	Norway	MI	Propranolol, placebo	560	Parallel	Yes	52	Yes	Cold hands and feet
Persson et al. [41]	Sweden	MI	Metoprolol, xamoterol	121	Parallel	No	52	Yes	Cold extremities
Greenberg et al. [42]	UK	HT	Propranolol, thiazide, placebo	7241	Parallel	No	256	No	Raynaud's phenomenon
BHATR Group [43]	USA	MI	Propranolol, placebo	3837	Parallel	Yes	109	Yes	Cold hands, feet
Silberstein et al. [44]	Norway	Migraine	Propranolol, placebo	191	Parallel	Yes	261	Yes	Peripheral coldness
Leren et al. [45]	France	Angina	Propranolol, α-adrenoceptor blocker	23	Crossover	No	8	Yes	Cold hands and feet
Pascal & Rales [46]	USA	VB	Propranolol, placebo	230	Parallel	Yes	62	No	Raynaud's phenomenon
Moltzer et al. [47]	Italy	HT	Metoprolol, ACE/ARB	16	Crossover	Yes	16	No	Cold extremities
Metra et al. [48]	Scotland	HF	Metoprolol, carvedilol	150	Parallel	Yes	100	Yes	Raynaud's phenomenon
Herrick et al. [49]	UK	HT	Atenolol, ACE/ARB	162	Parallel	Yes	12	Yes	Cold extremities
Taylor et al. [50]	UK	HF	Oxprenolol, placebo	1103	Parallel	No	209	Yes	Cold extremities
UKPDS [51]	Germany	DT2	Atenolol, ACE/ARB	758	Parallel	No	438	Yes	Cold hands and feet
The DTS Group [52]	Europe	MI	Atenolol, placebo	1473	Parallel	Yes	157	Yes	Cold extremities
The IPPPSH Group [53]	Sweden	HT	Oxprenolol, placebo	6357	Parallel	No	209	Yes	Cold extremities
Ekbom et al. [54]	Sweden	HT	Metoprolol, atenolol, pindolol, placebo	1021	Parallel	No	52	Yes	Cold hands and feet
Garden et al. [55]	UK	VB	Propranolol, placebo	81	Parallel	No	104	Yes	Cold extremities
Nielsen et al. [56]	Denmark	HT	Atenolol, ACE/ARB	36	Parallel	No	183	No	Cold extremities
Beevers et al. [57]	UK	HT	Atenolol, ACE/ARB, placebo	288	Parallel	Yes	8	Yes	Cold extremities
Khattar et al. [58]	UK	HF	Carvedilol, ACE/ARB	57	Parallel	No	12	Yes	Cold peripheries
Mc Neil et al. [59]	Australia	HT	Metoprolol, pindolol, atenolol, labetalol	29	Crossover	No	10	Yes	Cold extremities
Pasotti et al. [60]	Italy	HT	Pindolol, metoprolol	16	Crossover	Yes	12	Yes	Cold extremities
Iliuta et al. [61]	Romania	CABPG	Betaxolol, metoprolol	1352	Parallel	No	4	Yes	Cold extremities
Vandenburg et al. [62]	UK	HT	Propranolol, α-adrenoceptor blocker	60	Parallel	Yes	10	No	Cold extremities
Detry et al. [63]	International	Angina	Propranolol, trimetazidine	149	Parallel	Yes	12	Yes	Cold extremities
Salonen et al. [64]	Finland	HT	Betaxolol, placebo	60	Crossover	No	4	Yes	Cold hands and feet

(continues)

Table 1
(Continued)

Study	Country	Indication	Treatment	n	Methodology	Exclude RP	Exposure (weeks)	Double-blind	Peripheral vasoconstriction symptom
Bühler et al. [65]	Europe	HT	Bisoprolol, atenolol	94	Crossover	Yes	8	Yes	Cold extremities
De Muinck et al. [66]	Europe Nord	Angina	Bisoprolol, atenolol	175	Parallel	No	12	Yes	Cold extremities
Pedersen et al. [67]	Denmark	HT	Metoprolol, thiazide	20	Crossover	No	8	Yes	Cold extremities

HT: hypertension; MI myocardial infraction; HF heart failure; VB: variceal bleeding; T2DM: type two diabetes mellitus; CAPBG: coronary artery bypass grafting. CCB: calcium channel blockers; ACE/ARB: angiotensin converting enzyme inhibitors /angiotensin II receptor blockers.
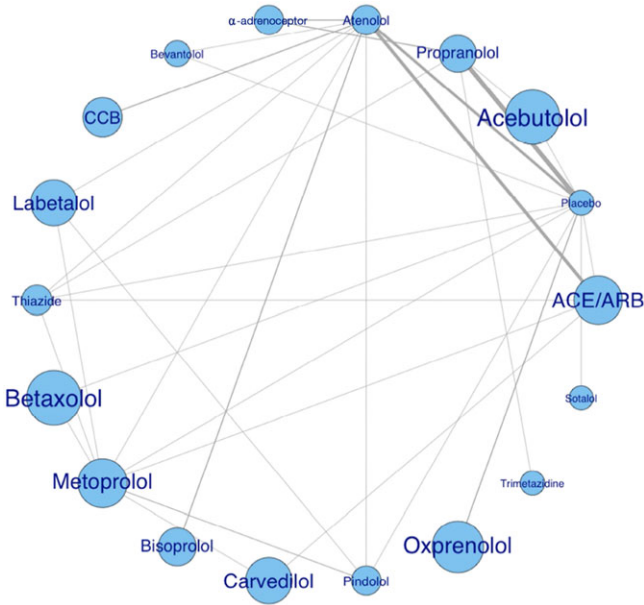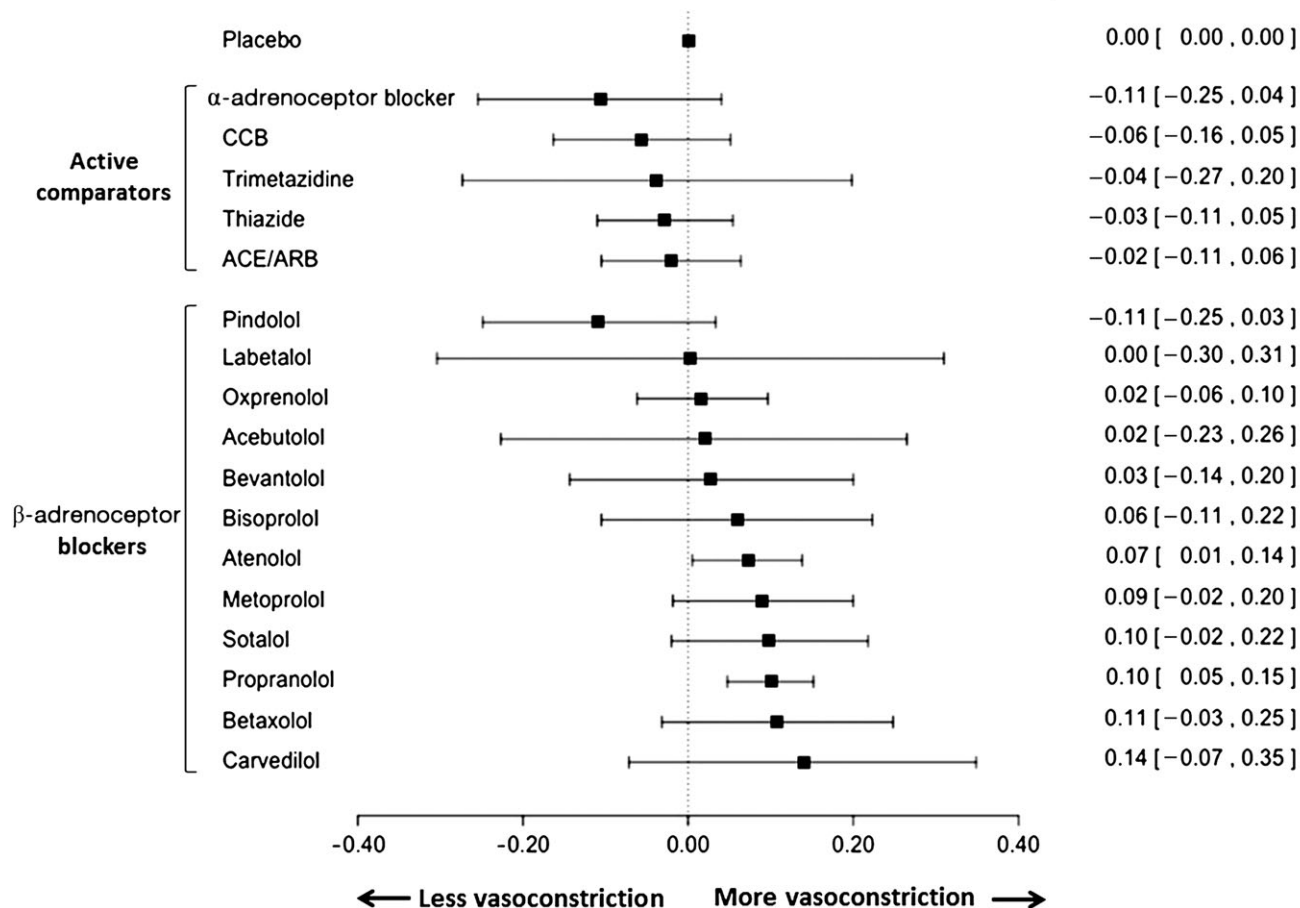

Figure 2

Network of available comparisons between the different β-adrenoceptor blockers and controls. Size of node is proportional to number of trials participants and thickness of the lines is proportional to number of trials that included the direct comparisons. CCB calcium channel blockers; ACE/ARB angiotensin converting enzyme inhibitors/angiotensin II receptor blockers

duration ($P = 0.06$), year of publication ($P = 0.19$), way of reporting adverse effect ($P = 0.39$) and RP as a non-inclusion criterion for the trial ($P = 0.21$).

Discussion

In our study 7% of the 28 072 patients taking β-adrenoceptor blockers suffered from RP or cold extremities, whereas only 4.6% did so when on placebo. We showed that β-adrenoceptor blockers represent a highly heterogeneous family regarding their propensity to induce RP, and some ancillary properties such as a vasodilator effect or ISA are somewhat protective, while $β_1$-selectivity is not.

The present work brings additional information to what was known about the prevalence of peripheral vasoconstriction induced by β-adrenoceptor blockers. The prevalence of 7% found in our study is lower than in the studies assessing it in the general population. A general practice based study in the UK found that 14.5% of patients responding to a postal survey and 19% of patients attending surgeries have RP-related symptoms. [68]. A community based study from the US reported RP in 11% of women and 8% of men [69]. In a recent meta-analysis, the prevalence of RP in patients receiving β-adrenoceptor blockers was 14.7% [8]. Included studies were clinical cohort, or case–control studies and for most of them RP symptoms were also reported using a questionnaire. This is close to what we found in studies reporting adverse effects with a questionnaire (prevalence of 13.5%) [38, 39, 53, 54, 56, 59, 65]. In this meta-analysis the influence of the way to report symptoms on the prevalence of

Figure 3

Forest plot, effect size estimated through the arcsin difference. CCB calcium channel blockers; ACE/ARB angiotensin converting enzyme inhibitors /angiotensin II receptor blockers

peripheral vasoconstriction was obvious (13.47% with a questionnaire *vs*. 6.02% for spontaneous reports), although non-significant, and should certainly be assessed in every meta-analysis focusing on side effects. Another explanation of the low prevalence observed in the present work was that RP was a non-inclusion criterion in 20 out of the 38 studies included. Although including or not patients with RP in trials obviously changes prevalence, it does not affect the general conclusion of the network meta-analysis. Finally, one should admit that there was considerable heterogeneity between studies [49, 56]. This variability probably reflects differences in the definition of RP or cold extremities and, in most cases, the lack of objective criteria to assess peripheral vasoconstriction.

Cold hands and RP were rapidly linked to the use of the first β-adrenoceptor blocker, propranolol [70]. Propranolol is a non-selective β_1- and β_2-adrenoceptor antagonist devoid of ISA and vasodilator activity. Activity on β_2-adrenoceptors was first incriminated in the pathophysiology of peripheral vasoconstriction related to β-adrenoceptor blocker intake. Indeed, β_2-adrenoceptors are involved in the vasodilator tone of blood vessels in skeletal muscle. However, studies did not show any difference in the frequency of the feeling of cold hands according to β_1-selectivity of β-adrenoceptor blockers [71–73]. Based on a large basis of available evidence, our study further shows that drugs with higher affinity for β_1- than for β_2-adrenoceptors, such as atenolol, also induce significantly more peripheral vasoconstriction than placebo.

There is also a rationale for a link between ISA and the reduction of peripheral vasoconstriction. Indeed, β-adrenoceptor blockers with ISA induce smaller falls in cardiac output and do not lead to the same baroreceptor-dependent reflex vasoconstriction as that observed with β-adrenoceptor blockers devoid of ISA [12, 74]. Pindolol is the β-adrenoceptor blocker with the highest ISA, followed by acebutolol, celiprolol and oxprenolol. Yet, in our study these β-adrenoceptor blockers are among those inducing the least peripheral vasoconstriction-related symptoms. This is consistent with experimental data showing that brachial artery infusion of pindolol leads to a dose-dependent increase of forearm blood flow, that may be reduced by concomitant infusion of propranolol [75]. The ISA of pindolol is so large that stimulation of β_2-adrenoceptors is produced, leading to vasodilatation and the relaxation produced by pindolol or celiprolol can partly be antagonized by pretreatment with propranolol or

Table 2

β-adrenoceptor blockers characteristics. We excluded β-adrenoceptor blockers used only for ophthalmic use in France: alprenolol, carteolol, levobunolol, metipranolol, penbutolol and timolol

β-adrenoceptor blocker	β_1-selectivity	ISA*	MSA**	Vasodilator activity	Half-life (h)	Mean usual hypertension dose (mg day^{-1})	Clinical application	Contra-indication with RP in USA	Contra-indication with RP in France	Contra-indication with RP in UK
•Propranolol	0	0	++	0	3.5–6	160	Hypertension, angina pectoris, migraine, hyperthyroidism, arrhythmias	No	Yes	Severe form
•Nadolol	0	0	0	0	14–24	160		No	Yes	No
•Sotalol	0	0	0	0	12	160–320		No	Yes	Yes
•Metoprolol	+	0	0	0	3–4	100–200	Hypertension, angina pectoris, arrhythmias	Severe form	Severe form	Severe form
•Atenolol	+	0	0	0	6–9	50–100		Precaution	Severe form	Severe form
•Betaxolol	+	0	0	Ca^{++} entry blockade	14–22	20		No	Severe form	Precaution
•Nebivolol	+	0	0	Nitric oxide release	11–30	5–10		Precaution	Severe form	Severe form
•Bisoprolol	+	0	0	0	9–12	5–10		Precaution	Severe form	Severe form
•Bevantolol	+	0	+	α$_1$-adrenoceptor blockade, Ca^{++} entry blockade	2	150–300		Not available	Not available	Not available
•Xamoterol	+	+	0	0				Not available	Not available	Not available
•Pindolol	0	++	0	0	3–4	15	Hypertension, migraine, arrhythmias	No	Yes	Yes
•Acebutolol	+	+	+	0	3–4	400		Precaution	Severe form	Severe form
•Oxprenolol	0	+	+	0	1–2	320		Not available	Yes	Severe form
•Celiprolol	+	+	−	β$_2$-adrenoceptor agonist, nitric oxide release	4–5	200–400		Not available	No	Severe form
•Carvedilol	0	0	0	α$_1$-adrenoceptor blockade, Ca^{++} entry, blockade, antioxidant activity	7–10	25–50	Heart failure	Precaution	Yes	Precaution
•Labetalol	0	0	0	α$_1$-adrenoceptor blockade	5	400	HTA	No	No	Severe form

0 = absent or low; + = moderate; ++ = high; − = no information; *ISA = intrinsic sympathomimetic activity; **MSA = membrane-stabilizing activity.
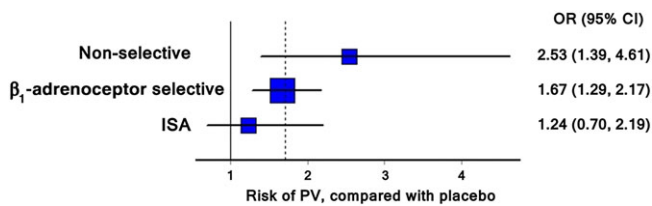
Figure 4

Comparison of the risk of peripheral vasoconstriction according to the pharmacological properties of β-adrenoceptor blockers. Only direct comparisons *vs.* placebo were included and a random effect model was used. ISA intrinsic sympathomimetic activity

sotalol [76–78]. Several clinical studies have previously reached similar conclusions. Direct comparison between pindolol and propranolol showed a decreased risk of peripheral vasoconstriction with pindolol [79]. A UK study including 7659 patients with hypertension in general practice found that peripheral vasoconstriction-related symptoms were more pronounced in patients taking β-adrenoceptor blockers than other hypertensive treatment (4.1% *vs.* 0.2%), but that patients taking β-adrenoceptor blockers with ISA complained less frequently than those on other β-adrenoceptor blockers (3.1% *vs.* 5.2%) [72].

Interestingly, in our study bevantalol and labetalol, two β-adrenoceptor blockers with vasodilator activity through α_2-adrenoceptor antagonism, are among drugs inducing the least peripheral vasoconstriction. In line with our results, α_2 adrenoceptor-induced vasoconstriction is increased in patients with Raynaud's phenomenon and selective inhibition of α_2-adrenoceptors reduces digital artery vasospastic attacks [2, 11]. Furthermore, we did not find any study implicating nebivolol and celiprolol, two β-adrenoceptor blockers with vasodilator activity through nitric oxide release, suggesting that patients taking these β-adrenoceptor blockers did not complain of peripheral vasoconstriction symptoms although large randomized controlled trials including thousands of patients and assessing the efficacy of nebivolol such as SENIORS study exist [80].

Overall, the results of this work challenge the relevance of the contraindication of β-adrenoceptor blockers in patients with peripheral vascular disease (Table 2). In the USA, propranolol, nadolol, sotalol, betaxolol, pindolol and labetalol are not contraindicated. Metoprolol is contraindicated in severe forms of peripheral circulatory disorder and precaution is recommended for atenolol, nebivolol, bisoprolol, acebutolol and carvedilol in patients with peripheral vascular disease. In France, carvedilol, nadolol, oxprenolol, pindolol, propranolol and sotalol are contraindicated in patients with RP. Acebutolol, betaxolol, bisoprolol, metoprolol and nebivolol are contraindicated only in severe forms, whereas celiprolol and labetalol are not contraindicated. It appears that contraindications vary between countries and that they do not seem to be based on available evidence.

Network meta-analysis is a relevant approach in pharmacovigilance, especially to test the homogeneity of a class adverse effect. Although this methodological approach is becoming more accessible thanks to the availability of dedicated statistics packages, its use remains limited in safety studies. The development of approaches and recommendations to appraise the quality of a treatment effect estimated

from a network meta-analysis participates toward standardizing practices. To our knowledge, this is the first network meta-analysis with a safety purpose that uses the GRADE recommendation to assess the quality of direct and indirect comparisons. This approach includes assessment of five items for each pairwise comparison: risk of bias [23], inconsistency [24], indirectness [25] and imprecision [26] and publication bias [27]. The risk of bias for each pairwise comparison was assessed in the light of the weight of each study involved, as advised in GRADE recommendations. In general, the risk of bias was relatively low in the studies that we included and overall the quality of direct comparisons was reasonable. Heterogeneity was >40% in only 2/34 pairwise comparisons reflecting consistency of our results. However, many pairwise comparisons based on indirect comparisons have a low level of evidence. The exchangeability property of the included studies in this network meta-analysis was respected because no interaction between the effect estimate and the factors known to modify the risk of peripheral vasoconstriction (e.g. duration of treatment, drug dose, drug indication, year of publication, way of reporting adverse effect and RP as a non-inclusion criterion for the trial) was highlighted in the sensivity analysis.

Another limitation is that we reduced our literature searches in the PubMed database to 'core clinical journals' only, possibly leading to a publication bias. However this study did not aim to assess an efficacy criterion of β-adrenoceptor blockers for which exhaustivity would have been mandatory. Indeed, we supposed that no clinical trial was unpublished or stopped because of RP or cold extremities. This restriction was imposed by the impressive amount of available data when considering β-adrenoceptor blockers. We were unable to consider all β-adrenoceptor blockers in our analysis, as well designed RCTs were lacking for some drugs.

Finally, the number of studies that reported peripheral vasoconstriction-related symptoms in the publication was low. Indeed, as it is often considered as well-known and benign, peripheral vasoconstriction-related symptoms may be omitted in study reports and thus only <5% of eligible studies were included in our analysis. This stresses the need for making data from clinical trials widely available for further analyses with safety purposes.

Conclusion

While peripheral vasoconstriction-related symptoms induced by β-adrenoceptor blockers have long been known to be side effects, this network meta-analysis provides evidence that this should not be considered as a homogeneous class effect. Ancillary properties such ISA and vasodilator effects are protective. On the other hand, a higher affinity for β_1-adrenoceptors does not protect from RP, which challenges current recommendations and contraindications.

Competing Interests

All authors have completed the Unified Competing Interest form and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work

in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Contributors

CK, TJ, SB, PC, JLC and MR wrote manuscript, MR designed research, CK and MR performed the research and TJ analyzed the data.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

http://onlinelibrary.wiley.com/doi/10.1111/bcp.12980/suppinfo.

Table S1 Quality ratings following GRADE recommendations for comparison of peripheral vasoconstriction induced by β-adrenoceptor blockers. CCB calcium channel blockers; ACE/ARB angiotensin converting enzyme inhibitors /angiotensin II receptor blockers

Table S2 Number of direct and indirect comparisons included in the network meta-analysis, average GRADE quality rating summary and percentage of high quality studies for each β-adrenoceptor blocker

Table S3 Number of direct and indirect comparisons included in the network meta-analysis, mean GRADE quality rating summary and percentage of high quality studies for each pharmacologic group of β-adrenoceptor blocker. ISA intrinsic sympathomimetic activity. VD vasodilator activity

Figure S1 The risk of bias summary

Figure S2 Rankograms represent for each treatment on the horizontal axis the 18 possible ranks (from left to right the risk of peripheral vasoconstriction decreases) and on the vertical axis the probability to achieve each rank. CCB calcium channel blockers; ACE/ARB angiotensin converting enzyme inhibitors/angiotensin II receptor blockers